CORRESPONDENCE

Re: Have We Resolved How To Triage Equivocal Cervical Cytology?

In their recent editorial, Solomon and Schiffman *(1)* commented on our meta-analysis of the accuracy of the human papillomavirus (HPV) DNA testing as an alternative to a repeat Pap smear to triage women with equivocal cervical cytology *(2)*. In general, they agreed with our conclusion that detection of high-risk HPV DNA using the Hybrid Capture 2 (HC2) assay (Digene, Gaithersburg, MD) predicts the presence or absence of cervical intraepithelial neoplasia of grade 2 or worse disease (CIN2+) more accurately than repetition of the Pap test. The pooled sensitivity and specificity of the HC2 assay were 95% (95% confidence interval [CI] = 92.7% to 96.9%) and 67% (95% CI = 58.2% to 76.4%), respectively. The sensitivity of the HC2 assay was 16% higher (ratio of HC2 assay to repeat cytology = 1.16, 95% CI = 1.04 to 1.29) than that of repeat cytology using atypical squamous cells of undetermined significance (ASCUS) or worse as the cut point, whereas the relative specificity did not differ significantly from unity (ratio = 1.05, 95% CI = 0.96 to 1.15).

Solomon and Schiffman *(1)* also had some criticisms. First, they questioned the inclusion criterion, presence of an index smear showing ASCUS, which is poorly reproducible. Second, they stated that, with rapidly evolving technologies, meta-analyses are quickly outdated. These issues have already been addressed in our discussion *(2)*. Then, they queried whether our meta-analysis considered issues of test quality. We did consider the influence of quality issues and refer readers to the pooled analysis by subgroups presented in table 6 *(2)* and to the multivariable meta-regression and SROC (Summary Receiver Operator Characteristic) regression presented elsewhere *(3)*. We would like to emphasize that a meta-analysis is not merely pooling data of homogenous datasets with the sole purpose of increasing power. In diagnostic research, absence of heterogeneity is rare, and one purpose of a meta-analysis is to explore sources of the heterogeneity by using formal statistical methods. By doing so, we were able to point out that the accuracy of older HPV DNA detection systems was lower than that of the HC2 assay and that our conclusions were robust over a wide range of clinical situations.

We agree with the remark made by Solomon and Schiffman that CIN3 or worse (CIN3+) is also a relevant outcome to evaluate triage methods. Therefore, we performed a pooled analysis of four studies that present data on the accuracy of HC2 for CIN3+ *(4–7)*. The sensitivity of HC2 varied from 93.3% to 100%, with a pooled estimate of 96.4% (95% CI = 93.5% to 99.9%) (Table 1). The specificity of HC2 varied from 45.8% to 69.7%, with a pooled estimate of 56.5% (95% CI = 45.5% to 67.5%). Only the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS) *(5)* documented the accuracy of repeat cytology for CIN3+, in which the sensitivity and specificity at a cutoff of ASCUS or worse were 85.3% (95% CI = 78.4% to 90.3%) and 42.7% (95% CI = 40.7% to 44.8%), respectively. The sensitivity at higher cytologic thresholds was substantially lower. The sensitivity of HC2 was 13% higher than that of repeat cytology at a cutoff of ASCUS or worse (ratio of 1.13, 95% CI = 1.05 to 1.22). Even the specificity of HC2 was 7% higher than that of repeat cytology at the ASCUS-or-worse cut point, and this difference in specificity was marginally statistically significant (95% CI = 1.00 to 1.14). Thus, we can conclude that high-risk HPV DNA detection using the HC2 assay is also more accurate than repeat cytology for predicting CIN3+ in women with a previous equivocal cervical smear.

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Table 1. Accuracy of the HC2 assay and of repeat cytology in triaging women with ASCUS for the presence and prevalence of CIN3+*

Study (ref)	Triage test cutoff	N	Sensitivity (95% CI)	Specificity (95% CI)	CIN3+ prevalence
		Triage test: HC2 assay			
Lin et al. *(4)*	0.2 pg/mL, RLU >1	74	1.000 (0.768 to 1.000)	0.583 (0.449 to 0.709)	0.189
Solomon et al. *(5)*	1 pg/mL, RLU >1	2310	0.963 (0.916 to 0.988)	0.458 (0.437 to 0.479)	0.059
Ziclinski et al. *(6)*	1 pg/mL, RLU >1	213	1.000 (0.398 to 0.665)	0.665 (0.597 to 0.729)	0.019
Lonky et al. *(7)*	1 pg/mL, RLU >1	213	0.933 (0.681 to 0.998)	0.697 (0.628 to 0.760)	0.070
Pooled		2810	0.964† (0.935 to 0.999)	0.565‡ (0.455 to 0.675)	0.057
		Triage test: repeat cytology			
Solomon et al. *(5)*	ASCUS	2317	0.853 (0.784 to 0.903)	0.427 (0.407 to 0.448)	0.059
Solomon et al. *(5)*	LSIL	2317	0.640 (0.557 to 0.716)	0.759 (0.740 to 0.776)	0.059
Solomon et al. *(5)*	HSIL	2317	0.441 (0.360 to 0.525)	0.954 (0.945 to 0.962)	0.059

*HC2 = hybrid capture 2 assay; ASCUS = atypical squamous cells of unspecified significance; CIN3+ = cervical intracpithelial lesions, grade 3 or worse; CI = confidence interval; RLU = relative light unit; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion. The viral load, measured with the HC2 assay, is expressed in units of relative light intensity and computed using a chosen control, which contains a known concentration of human papillomavirus DNA (in pg/mL).

†A fixed model was used to pool sensitivity measures because of a lack of statistically significant interstudy heterogeneity ($P = .89$).

‡A random effect model was used to pool the specificity measures because of statistically significant interstudy heterogeneity ($P < .001$).

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RESPONSE

We thank Arbyn and colleagues for providing an analysis using a stringent outcome of cervical intraepithelial neoplasia grade 3 precancer or cancer to evaluate triage strategies. From their useful analysis and other evidence, we agree with their conclusions regarding the triage of equivocal cytology by testing for oncogenic types of human papillomavirus (HPV).

We have a remaining methodologic difference of opinion with Arbyn and colleagues regarding the use of heterogeneous datasets in meta-analyses. In our editorial, we questioned the inclusion of studies that relied on obsolete HPV tests. We raise this point again for consideration because the optimal analysis of improving measurements is a general problem inherent to meta-analyses of rapidly evolving technologies. In their analysis, Arbyn and colleagues included HPV tests that are no longer manufactured because of documented poorer performance than the current Food and Drug Administration–approved kit and comparable, well-validated polymerase chain reaction–based assays *(1,2)*. In defending their thoroughness, Arbyn et al. responded that "absence of heterogeneity is rare, and one purpose of a meta-analysis is to explore sources of the heterogeneity using formal statistical methods." In our opinion, considering obsolete testing strategies is a diversion from the job of clarifying the performance of current assays. The performance of triage using an inferior HPV test does not inform about the performance of triage using state-of-the-art tests. Misclassification resulting from obsolete HPV tests obscures the risk relationships and clinical usefulness of HPV testing *(2–4)*. Because there is little to be learned by studying obsolete tests that will never be used again, we favor meta-analyses that begin by including only viable testing options, regardless of worthy characteristics of the older published studies.

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